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Docket No.

56U29/4356

**TRANSMITTAL OF INFORMATION DISCLOSURE STATEMENT**  
 (Under 37 CFR 1.97(b) or 1.97(c))

In Re Application:

Rice et al.

Serial No.  
09/578,989Filing Date  
05/23/2000Examiner  
Wortman, Donna C.Group Art Unit  
1648

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Sheet 1 of 1

**INFORMATION DISCLOSURES STATEMENT BY APPLICATION**  
(use as many sheets as necessary)

Docket Number (Optional)  
56029-4356

Application Number  
09/578,989

Applicant  
Rice et al.

Filing Date  
May 23, 2000

Group Art Unit  
1642

U.S. PATENT DOCUMENTS						
EXAMINER INITIAL	RFF	DOCUMENT NUMBER	ISSUE DATE	NAME	CLASS    SUBCLASS	
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FOREIGN PATENT DOCUMENTS						
REF	DOCUMENT NUMBER	ISSUE DATE	COUNTRY	CLASS    SUBCLASS	TRANSLATION YES NO	
<b>OTHER DOCUMENTS</b> (Including Author, Title, Date, Pertinent Pages, Etc.)						
EH	Frolov et al., J. Virol., Vol. 72, Selection of RNA replicons capable of noncytopathic replication in mammalian cells; pages 3854-3856; 1999					
EI	Janssen et al., Virology, Vol. 163, Complete nucleotide sequence of a cell culture-adapted variant of hepatitis A virus: comparison with wild-type virus with restricted capacity for in vitro replication, pages 299-307, 1988.					
EJ	Krieger et al., J. Virol., Vol. 75, Enhancement of Hepatitis C Virus RNA replication by cell culture-adaptive mutations, pages 4614-4624, 2001.					
EK	Lochmann et al., J. Virol., Vol. 75, Mutations in Hepatitis C Virus RNAs conferring cell culture adaptation, pages 1437-1449, 2001.					
EL	Lundkvist et al., J. of Virol., Vol. 71, Cell culture adaptation of puumala hantavirus changes the infectivity for its natural reservoir, Clethrionomys glareolus, and leads to accumulation of mutants with altered genomic RNA 3 segment, pages 9515-9523, 1997.					
EXAMINER						DATE CONSIDERED

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Rice et al.	Group No.:	1648
Serial No.:	09/576,989	Atty. Docket No.:	56029-4356
Filed:	05/23/2000	Examiner:	Wortman, Donna C.
For:	HCV Variants		

Commissioner of Patents and Trademarks  
Washington, DC 20231

AMENDMENT AND RESPONSE

HONORABLE SIR:

Responsive to the official communication of December 3, 2002, Applicant submits the following Amendments and Remarks.

It is not believed that extensions of time are required beyond those which may otherwise be provided for in documents accompanying this Amendment. However, in the event that additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned for under 37 C.F.R. § 1.136(a), and any fees required therefore are hereby authorized to be charged to our Deposit Account 20-0823.

Please amend the above-identified application as set forth below.

*In The Specification:*

Please amend the specification as indicated:

At page 1, after the title and before the heading "Background of the Invention" insert the following paragraph:

—This application is a continuation in part of prior U.S. application Serial No. 09/034,756, filed March 4, 1998, now U.S. Patent No. 6,392,028, issued May 21, 2002; which is a continuation of U.S. application Ser. No. 08/811,566, filed March 4, 1997, now U.S. Patent No. 6,127,116, Issued October 3, 2000; which claims priority to Provisional application Ser. No. 60/039,843, filed March 4, 1997, now abandoned.—

At page 2 please replace the paragraph beginning at line 11 with the following paragraph:

—Although Interferon (IFN)- $\alpha$  has been shown to be useful for the treatment of a minority of patients with chronic HCV infections [Davis et al., N. Engl. J. Med. 321, 1501-1506 (1989); DiBisceglie et al., N. Engl. J. Med. 321, 1506-1510 (1989)] and subunit vaccines show some promise in the chimpanzee model [Choo et al., Proc. Natl. Acad. Sci. USA 91, 1294-1298 (1994)], future efforts are needed to develop more effective therapies and vaccines. The considerable diversity observed among different HCV isolates [for review, see Bukh et al., Sem. Liver Dis. 15, 41-63 (1995)], the emergence of genetic variants in chronically infected individuals [Enomoto et al., J. Hepatol. 17, 415-416 (1993); Hijikata et al., Biochem. Biophys. Res. Comm. 178, 220-

228 (1991); Kato et al., *Biochem. Biophys. Res. Comm.* **189**, 119-127 (1992); Katu et al., *J. Virol.* **67**, 3923-3930 (1993); Kurosaki et al., *Hepatology* **18**, 1293-1299 (1993); Lesniewski et al., *J. Med. Virol.* **40**, 150-156 (1993); Ogata et al., *Proc. Natl. Acad. Sci. USA* **88**, 3392-3396 (1991); Weiner et al., *Virology* **180**, 842-848 (1991); Weinor et al., *Proc. Natl. Acad. Sci. USA* **89**, 3468-3472 (1992)], and the lack of protective immunity elicited after HCV infection [Farci et al., *Science* **258**, 135-140 (1992); Prince et al., *J. Infect Dis.* **165**, 438-443 (1993)] present major challenges towards these goals. -

**In The Claims:**

Please amend the claims as indicated:

Cancel claims 10, 11, 18-24, 41-44 and 63-68.

1. (Four times amended) A polynucleotide comprising a non-naturally occurring HCV sequence that is capable of productive replication in a host cell, or is capable of being transcribed into a non-naturally occurring HCV sequence that is capable of productive replication in a host cell, wherein the HCV sequence comprises, from 5' to 3' on the positive-sense nucleic acid, a functional 5' non-translated region (5' NTR); one or more protein coding regions, including at least one polyprotein coding region that is capable of replicating HCV RNA; and a functional HCV 3' non-translated region (3' NTR), wherein said polynucleotide further comprises an adaptive mutation in the NS5A coding region that confers improved cell culture characteristics to said polynucleotide.

76. (New) The polynucleotide of claim 1, further comprising a mutation in the NS3 or NS4B coding region.

**REMARKS**

The specification has been amended to contain a specific reference to earlier parent applications and their current status in the first sentence. Also, as requested by the Examiner, the reference to hyperlinks and/or other forms of browser-executable code at page 2, line 19 has been deleted from the specification. The claims have been amended as indicated above.

The Office asserts at page 5, paragraph 2 of the Office Action that the IDS filed April 4, 2002 fails to comply with 37 C.F.R. §1.97(c). In order to remedy that deficiency, the IDS is herewith resubmitted with the appropriate fee.

Claim 9 is rejected under 35 U.S.C. §112, second paragraph as being indefinite. Specifically, the Office indicates that since applicant has stated in a previous submission that "The invention is not directed to mutations that cause the polynucleotide to have attenuated virulence, as indicated by the amendment to claim 1," and since claim 9 recites viral properties that correspond to attenuated virulence, that claim 9 fails to correspond in scope with that which applicants regard as the invention. Note, however, that claim 9 is dependent on claim 1, which is directed to a polynucleotide which comprises, among other things, an adaptive mutation in the NS5A coding region that confers improved cell culture characteristics. Thus, claim 9 is directed to a polynucleotide that comprises an NS5A mutation that confers improved cell culture characteristics, and further comprises characteristics consistent with attenuated virulence. Therefore, claim 9 is directed to various species within the scope of generic claim 1. As such, claim 9 is definite and does set forth subject matter which applicant regards as their invention.

Claims 1, 3-4, 29, 61, 62, 69, 70 and 72-75 are rejected under 35 U.S.C. §112, first paragraph as lacking enablement. Specifically, the Office alleges that while the specification is enabling for a polynucleotide comprising a non-naturally occurring HCV sequence capable of productive replication in a host cell that comprises an adaptive mutation of the NS5A gene that confers improved cell culture characteristics to the polynucleotide, it does not reasonably provide enablement for adaptive mutations other than a mutation of the NS5A gene. While applicant respectfully disagrees with that

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statement, in the interest of expediting prosecution of the instant application, claim 1 has been amended to include a limitation that the adaptive mutation is "in the NS5A coding region." In light of that amendment, applicant respectfully requests that this rejection be withdrawn.

Claims 1, 7, 9-11, 61, 62, 69, 70 and 72-74 are rejected under 35 U.S.C. §102(e) as being anticipated by Yanagi et al. for reasons of record. In the Office Action dated January 10, 2002, the Office cites Yanagi as teaching an isolated and purified polynucleotide that is capable of productive replication in a host cell in which all or part of the portion of the polynucleotide encoding the NS5A protein is deleted, and that deletions in the polynucleotides encoding the infectious nucleic acid sequences may be made in order to produce attenuated HCV for vaccine development.

First, by the Office's admission (O/A of 1/10/02 at page 11), Yanagi does not teach that mutations may be made in order to confer improved cell culture characteristics. The instant claims are limited to those polynucleotides that comprise "an adaptive mutation that confers improved cell culture characteristics..." Contrary to the Office's position that applicant is relying on limitations not found in the claims, claim 1 as pointed out above, is limited to polynucleotides with improved cell culture characteristics, and therefore is not anticipated by Yanagi.

Next, the Office states in the Action dated January 10, 2002 (at page 11) that "while Yanagi et al. are silent as to the transfection efficient of the polynucleotides into mammalian cells, absent some evidence to the contrary, polynucleotides having the recited structure of a functional 5' non-translated region,..., and a deletion of a portion of all of the NS5A protein would inherently possess" improved cell culture characteristics.

The Office has not made a reasonable showing that the inherency rejection is supportable. In *Ex parte Skinner*, 2 USPQ2d 1788, 1789 (Bd. Pat. App. & Interf. 1986) the Board stated:

"[W]here an examiner has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, the examiner possesses the authority to require an applicant to prove that the subject matter shown to be in the prior art does not possess the

characteristic relied on. Nevertheless, before an applicant can be put to this burdensome task, the examiner must provide some evidence or scientific reasoning to establish the reasonableness of the examiner's belief that the functional limitation is an inherent characteristic of the prior art. In the case before us, no such evidence or reasoning has been set forward." (emphasis added).

In the instant case, the Office has merely stated that absent any evidence to the contrary, the polynucleotides disclosed in Yanagi et al. would inherently possess improved cell culture characteristics. That statement is neither evidence nor a reference to any evidence. That statement is also not scientific reasoning. No reason is given as to why the polynucleotides of Yanagi et al. may possess the improved cell culture characteristics of the instant claims. The allegation that the polynucleotides disclosed by Yanagi et al. may possess such characteristics fails to establish anticipation. The mere fact that a certain thing may result from a given set of circumstances is insufficient to prove anticipation. *Electro Medical Systems, S.A. v. Cooper Life Sciences, Inc.*, 32 USPQ2d 1017 (Fed. Cir. 1994); *Continental Can Co. USA, Inc. v. Monsanto Co.*, 20 USPQ2d 1746 (Fed. Cir. 1991).

To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *In re Oerlich*, 212 USPQ 323 (CCPA 1981); *In re Robertson*, 49 USPQ2d 1949, 1950 (Fed. Cir. 1999). The evidence of record, cited by the Office at pages 5-6 of the Action dated December 3, 2002, according to the Office, indicates that "...Yanagi only speculates where adaptive mutations might be found; this speculation has been relied upon to support the Examiner's position that the location of such mutations is unpredictable."

Further, the Office states that "[r]eview of the documents of Lundkvist et al.; Frolov et al.; and Jansen et al. ... is not seen to provide any support for predictability for locating cell culture-adaptive mutations in HCV." Given this unpredictability, it is speculative at best, as to whether the polynucleotides of Yanagi et al. would possess

improved cell-culture characteristics. *In re Robertson*, 49 USPQ2d 1049, 1951 (Fed. Cir. 1999) ("Inherency, however, may not be established by probabilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.").

Thus, the Office has not carried its burden of establishing a *prima facie* case of anticipation by inherency. MPEP §2112. The burden of proof is on the Office to provide evidence or scientific reasoning showing that the claimed "improved cell culture characteristics" are inherently possessed by the polynucleotides taught by Yanagi et al. Absent any such evidence or reasoning in the instant case, and in the face of contradictory evidence, the Office has not met its burden to establish *prima facie* anticipation, and has improperly shifted the burden to Applicant to show an unobvious difference between the polynucleotides of Yanagi et al. and those claimed in the instant application. MPEP §2112. Therefore, the rejection under 35 U.S.C. §102(e) must be withdrawn.

Claims 3-6 and 29 are rejected under 35 U.S.C. §102(e) as being anticipated by, or in the alternative, under 35 U.S.C. §103(a) as being obvious over Yanagi et al. for reasons of record. In the Office Action dated January 10, 2002, the Office cites Yanagi as teaching polynucleotides that "inherently possess" improved cell culture characteristics.

Claims 8 and 76 are rejected under 35 U.S.C. §103(a) as being unpatentable over Yanagi et al. in view of Mizuno et al. for reasons of record. In the Office Action dated January 10, 2002, the Office cites Yanagi as teaching polynucleotides that "inherently possess" improved cell culture characteristics.

As both of the above rejections under 35 U.S.C. §102(e)/103(a) rely on Yanagi et al. as teaching polynucleotides that "inherently possess" improved cell culture characteristics, they must be withdrawn, because as discussed above, the Office has failed to present a *prima facie* case as to the allegedly inherent characteristic of the polynucleotides taught by Yanagi et al.

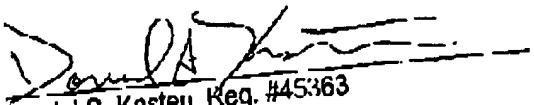
In addition, the Office mentions at page 7, that at least claim 9 presently reads on attenuating mutations. It is not clear why that statement appears in this context, as claim 9 was not rejected under 35 U.S.C. §102 or §103. However, that statement has

no bearing on the patentability of claim 9, because as with all of the claims in the instant application, claim 9 requires an "adaptive mutation in the NS5A coding region that confers improved cell culture characteristics." Therefore, the polynucleotides of Yanagi et al. cannot anticipate or render obvious any of those claims, as discussed above.

*I. Conclusion*

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action, and as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, she is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment is respectfully requested.  
Respectfully submitted,

  
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**Clean version of amended claims:**

1. A polynucleotide comprising a non-naturally occurring HCV sequence that is capable of productive replication in a host cell, or is capable of being transcribed into a non-naturally occurring HCV sequence that is capable of productive replication in a host cell, wherein the HCV sequence comprises, from 5' to 3' on the positive-sense nucleic acid, a functional 5' non-translated region (5' NTR); one or more protein coding regions, including at least one polyprotein coding region that is capable of replicating HCV RNA; and a functional HCV 3' non-translated region (3' NTR), wherein said polynucleotide further comprises an adaptive mutation in the NS5A coding region that confers improved cell culture characteristics to said polynucleotide.

76. The polynucleotide of claim 1, further comprising a mutation in the NS3 or NS4B coding region.

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